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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/024,988
Filing Date: February 17, 1998
Appellant(s): NELSON ET AL.

Laura J. Zeman
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 3/19/2007 appealing from the Office action mailed 3/10/2006.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

An appeal currently pending in relation to Serial No. 09/808,314, which has been assigned Appeal No: 2007-3937.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct, except for the indication of which claims are pending. The following is the correct status of the claims:

Claims 1-30, and 41 are canceled.

Claims 31-40 and 42-50 are pending.

Claims 32, 34-39 and 42-47 are withdrawn from consideration.

Claims 31, 33, 40 and 48-50 stand rejected under 35 U.C.C. 103(a).

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct in that the claims pending on appeal are outlined with specific references to the specification of the patent application. However, the examiner disagrees with two of the statements on page 3 of the Brief.

Appellant states that the claimed subject matter relates to methods for quantifying the relative amount of one or more analytes (antigens or antibodies) present in a specimen, and that analytes contained within a specimen are captured and isolated from another analyte and then mass spectrometrically analyzing the isolated analyte *after releasing it from the capturing agent* [emphasis added]. However, the claims are not so limited. The claims do not recite any steps that would limit the methods to those where the analyte is mass spectrometrically analyzed only after it is released from the capturing agent.

Appellant also states that the claimed subject matter relates in part to methods where the internal reference species (IRS) is not a modified variant of the analyte, and that another immunochemical affinity group must be present in the affinity reagent in order to simultaneously capture and isolate the internal reference species along side the analyte. However, the claimed methods relate only to methods where the IRS is "a modified analyte with shifted molecular weight *that binds to the affinity reagent*"(claim 31, emphasis added), or the IRS is "a modified protein with shifted molecular weight *that binds to the affinity reagent"* (claim 48, emphasis added).

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

Grounds of Rejection Not on Review

The following grounds of rejection have not been withdrawn by the examiner, but they are not under review on appeal because they have not been presented for review in the appellant's brief: Obviousness-type double patenting.

Claims 31, 33, 40 and 48-50 remain provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 31, 33, 37, 39, 44, 46 of copending Application No. 09/808,314, filed 3/14/2001.

Although the conflicting claims are not identical, they are not patentably distinct from each other because claims 31, 33, 37, 39, 44, 46 of copending Application No. 09/808,314 are drawn to methods for determining how much of, or the relative amount of, one or more certain antigens (or antibodies or analytes) are present in a sample, comprising the steps of adding an internal reference species (where the internal reference species binds to the same affinity reagent as the analyte) to the sample, and appears to comprise a step of using matrix-assisted laser desorption/ionization (MALDI) mass spectrometry to quantify the signals of the antigens, antibodies or analytes together with the internal reference species (claim 31, for example, contains the step of "adding a laser desorption/ionization agent to the released one or more analytes..."). Therefore, the claims of 09/808,314 appear to be encompassed by claims 31, 33, 40, and 48-50, because these claims are drawn to methods for quantifying analytes or proteins in a sample, comprising the addition of an internal reference species that binds to an affinity reagent that also binds to the analyte and the use of MALDI for analyzing and quantifying the analyte.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Non-appealable Issues

At pages 15-16 of the Brief (bridging paragraph), appellants discuss the propriety of making the Office action mailed 3/10/2006 final. This issue relates to petitionable subject matter under 37 CFR 1.181 and not to appealable subject matter. See MPEP § 1002 and § 1201.

At pages 8 (section VII. ARGUMENT) to page 12, first line, appellants present arguments having to do with whether appellants' amendments after final raise new issues under 35 USC 112. Appellants also enclose a copy of the proposed amended claims (starting on page 9 of the Brief). Appellants are referred to the MPEP 1205.02, which states that the brief must be directed to the claims and to the record of the case as they appeared at the time of the appeal. Furthermore, MPEP 1205.02 points to 37 CFR 41.37(c) (2) which prohibits the inclusion in a brief of any new or non-admitted amendment, affidavit or other evidence.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

U.S. 6,528,320 Hutchens 3-2003

Duncan, M.W. "Quantitative Analysis of Low Molecular Weight Compounds of Biological Interest by Matrix-Assisted Laser Desorption Ionization", Rapid Communications in Mass Spectrometry, Vol. 7, (1993), pp. 1090-1094.

Nuwaysir, L.M. "Electrospray Ionization Mass Spectrometry of Phosphopeptides Isolated by On-Line Immobilized Metal-Ion Affinity Chromatography", J. Am. Soc. Mass Spectrom., Vol. 4 (1993), pp. 662-669.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 31, 33, 40, 48, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan (Duncan, M.W. et al., Rapid Communications in Mass Spectrometry, 7: 1090-1094, 1993) in view of Nuwaysir (Nuwaysir, L.M., et al. J. Am. Soc. Mass Spectrom., 4: 662-669, 1993).

Duncan teaches a method for quantifying analytes comprising the steps of combining a specimen with an internal reference species (page 1090, 1st column, 2nd paragraph – 2nd, column) and then analyzing the resulting mixture by matrix-assisted laser desororption ionization (MALDI). Duncan teaches analytes such as acetylcholine, dihydroxyphenylalanine and a peptide, H-Ser-Ala-Leu-Arg-His-Tyr-NH_2 (see page 1090-1091, bridging paragraph). In the method of Duncan, the internal reference species (IRS) is an isotopically labeled analogue of the analyte (falls with the scope of "modified analyte with shifted molecular weight") or a structural analogue (see page 1090-1091, bridging paragraph). Duncan teaches that an IRS species for a peptide may be an isotopically labeled species in the case of lower molecular weight species, or a structural analog in the case of higher molecular weight species (see page 1092, 2nd column, 2nd paragraph). Duncan teaches analyzing and quantifying an analyte MALDI to resolve a distinct

signal for the analyte and the IRS, and then determining the ratio of the analyte signal to the IRS signal (see Figures 1 and 2 on page 1092). The standard curve presented in Figure 2 falls with in the scope of a working curve analysis of claims 33, 40, 49 and 50, because Duncan teaches making a plurality of standard preparations, each containing a known but differing concentration of the analyte (or protein), and each containing a known concentration of IRS; obtaining respective mass spectra of each of the plurality of standard preparations; normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum; creating a working curve by equating the normalized protein signals to the protein concentration of the plurality of standard preparations; obtaining a mass spectrum of the IRS-containing specimen; normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and quantifying the concentration of the analyte (or protein) in the specimen using the working curve (see page 1091, 2nd column, 2nd paragraph, and legend of Figure 2).

Duncan suggests that in the performance of quantitative analysis of "real" samples, of-line chromatography or immunoaffinity separations be used as a clean-up step (see page 1094). However, Duncan does not actually demonstrate a method in which such a clean-up step is performed in conjunction with steps of combining a specimen with an IRS and analyzing and quantifying an analyte to resolve distinct signal for the analyte and the IRS to determine the ratio of the analyte signal to the IRS signal.

However, Nuwaysir teaches a method of using metal-ion affinity chromatography to purify samples containing phosphopeptides before they are analyzed by MALDI for the purpose of determining the structure of the phosphopeptides (see page 663, 1st column, last paragraph

and page 665, 1st column, 3rd paragraph, see page 668, Figure 6). The samples are of phosphopeptides, which is encompassed by the term "protein" in claims 48-50.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the method of Duncan, which directed one to the use of isotopically labeled internal standards for quantification of analytes in the practice of MALDI, with the method of Nuwaysir on the use of affinity chromatography for the purification of samples prior to MALDI. The isotopically labeled internal standards of Duncan are examples of IRS species that have a shifted molecular weight compared to the analyte, and which would bind to an affinity reagent that also binds to the analyte (see Duncan, where isotopically labeled DOPA ([$^{13}C_6$]DOPA) is described as chemical mimic of DOPA, page 1092, 1st to 2nd column, bridging paragraph). The motivation to combine the teachings of the two references is provided by Duncan, in the contemplation of the necessity of a clean-up step that would encompass the use of immunoaffinity chromatography.

Claims 31, 33, 40, 48, 49 and 50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Duncan (Duncan, M.W. et al., Rapid Communications in Mass Spectrometry, 7: 1090-1094, 1993) in view of Hutchens (US 6,528,320; Mar. 4, 2003; effective filing date May 28, 1993).

Duncan teaches a method for quantifying analytes comprising the steps of combining a specimen with an internal reference species (page 1090, 1st column, 2nd paragraph – 2nd, column) and then analyzing the resulting mixture by matrix-assisted laser desororption ionization (MALDI). Duncan teaches analytes such as acetylcholine, dihydroxyphenylalanine and a

peptide, H-Ser-Ala-Leu-Arg-His-Tyr-NH_2 (see page 1090-1091, bridging paragraph). In the method of Duncan, the internal reference species (IRS) is an isotopically labeled analogue of the analyte (falls with the scope of "modified analyte with shifted molecular weight") or a structural analogue (see page 1090-1091, bridging paragraph). Duncan teaches that an IRS species for a peptide may be an isotopically labeled species in the case of lower molecular weight species, or a structural analog in the case of higher molecular weight species (see page 1092, 2nd column, 2nd paragraph). Duncan teaches analyzing and quantifying an analyte MALDI to resolve a distinct signal for the analyte and the IRS, and then determining the ratio of the analyte signal to the IRS signal (see Figures 1 and 2 on page 1092). The standard curve presented in Figure 2 falls with in the scope of a working curve analysis of claims 33, 40, 49 and 50, because Duncan teaches making a plurality of standard preparations, each containing a known but differing concentration of the analyte (or protein), and each containing a known concentration of IRS; obtaining respective mass spectra of each of the plurality of standard preparations; normalizing each of the mass spectra from the plurality of standard preparations by dividing each mass spectrum by the IRS signal within the mass spectrum; creating a working curve by equating the normalized protein signals to the protein concentration of the plurality of standard preparations; obtaining a mass spectrum of the IRS-containing specimen; normalizing the mass spectrum of the IRS-containing specimen by dividing by the IRS signal within the mass spectrum; and quantifying the concentration of the analyte (or protein) in the specimen using the working curve (see page 1091, 2nd column, 2nd paragraph, and legend of Figure 2).

Duncan suggests that in the performance of quantitative analysis of "real" samples, of-line chromatography or immunoaffinity separations be used as a clean-up step (see page 1094).

However, Duncan does not actually demonstrate a method in which such a clean-up step is performed in conjunction with steps of combining a specimen with an IRS and analyzing and quantifying an analyte to resolve distinct signal for the analyte and the IRS to determine the ratio of the analyte signal to the IRS signal.

However, Hutchens teaches a method of capturing an analyte from a sample on a sample presenting surface derivatized with an affinity reagent that binds the analyte, wherein the affinity reagent is a metal ion, a protein , a peptide, a nucleic acid or a dye, followed by detecting the capture analyte by laser desorption/ionization mass spectrometry (see claim 1, column 14). The analyte may be a protein (see claim 11, column 15).

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have combined the method of Duncan, which directed one to the use of isotopically labeled internal standards for quantification of analytes in the practice of MALDI, with the method of Duncan, directed to the use of affinity reagents present on a sample presenting surface of a laser desorption/ionization mass spectrometer, which allows one to capture an analyte from a sample. The isotopically labeled internal standards of Duncan are examples of IRS species that have a shifted molecular weight compared to the analyte, and which would bind to an affinity reagent that also binds to the analyte (see Duncan, where isotopically labeled DOPA ([$^{13}C_6$]DOPA) is described as chemical mimic of DOPA, page 1092, 1st to 2nd column, bridging paragraph). The motivation to combine the teachings of the two references is provided by Duncan, in the contemplation of the necessity of a clean-up step that would encompass the use of immunoaffinity chromatography.

(10) Response to Argument

A. Amendment After Final

The arguments presented in this section relate to an amendment that was not entered. Therefore, these arguments will not be addressed because they relate to claims that are not under appeal.

B. Establishment of a Prima Facie Case of Obviousness

Appellants argue that the examiner has failed to establish that the Duncan and Nuwaysir references or the Duncan and Hutchens references recite all of the claim elements including the exlusive steps of capturing the analyte and an internal reference species (IRS) with an affinity reagent, releasing the analyte and IRS from the affinity reagent and then analyzing and quantifying the analyte using matrix-assisted laser desorption/ionization (MALDI) on the released analyte and IRS. However, the claims under appeal to do not recite a step of releasing the analyte and IRS from the affinity reagent. Therefore, the examiner does not have to supply references that teach such a step. However, it is noted that in Nuwaysir, affinity chromatography is used in the step of combining a sample with an affinity reagent. Affintity chromatography is a process that results in the release of an analyte from an affinity reagent, because in affinity chromatography, first an analyte is bound to a matrix bearing an affinity molecule (e.g. antibody that binds the analyte of interest), and then buffers are applied to selectively remove impurities and then finally to disassociate the analyte from the affinity molecule. Further it is noted that the specification teaches a "disassociation agent", which is "any active cause which disassociates or unbinds a capture analyte from the affinity reagent. A laser desorption/ionization agent may also

act as a disassociation agent (see page 12, final paragraph of the specification). Therefore, Hutchens also appears to provide a method that would result in the release of the analyte from the affinity reagent, because release of the analyte from the affinity reagent may be accomplished through the process of laser desorption/ionization.

Appellants also state that the sample of the claimed methods does not undergo any additional prior clean-up or purification such as affinity chromatography as disclosed by Nuwaysir. This statement appears to contradict the claims and the specification, because the because the claims recite methods having a step of combining a sample with an affinity reagent, which is a step that results in the capturing an isolation of an analyte from other elements within a specimen. Furthermore, "affinity reagent" is a broad term that encompasses molecules such as antibodies and also antibodies attached to columns (e.g. columns used in affinity chromatography methods).

Appellants argue that the examiner has failed to establish a prima facie case of obviousness with the combination of Duncan and Nuwaysir. To support this argument, appellants state that "applicants have amended their claims by further limiting the claim language to show that quantification of the analyte is done by capturing the analyte and an internal reference species (IRS) with an affinity reagent, releasing the analyte and IRS from the affinity reagent, and then analyzing and quantifying the analyte using matrix-assisted laser desorption/ionization (MALDI) on the released analyte and IRS" (page 14, 2nd paragraph of the Brief). However, this is not persuasive because this argument relates to claim limitations that are not present in the claims under appeal. Appellants also conclude that "since neither Duncan nor Nuwaysir, either alone or in combination, disclose Applicants' discrete steps for quantifying

an analyte in a specimen, then applicants' claimed method cannot be obvious in light of Duncan and Nuwaysir". Assuming that the discrete steps referred to by appellants in their arguments are those recited in steps "c" of claims 31 or claim 48, and further set forth in the substeps outlined in claims 40 and 50, appellants argument is not convincing because the discrete steps for quantifying an analyte in a specimen using MALDI in combination with the step of adding an IRS to a sample are specifically taught in Duncan (see page 1091, 2nd column, 2nd paragraph, Figures 1 and 2, and legend of Figure 2 on page 1092).

Appellants also ague that the examiner has failed to establish a prima facie case of obviousness with the combination of Duncan and Hutchens. Again, appellants rely on the argument that the combination of Duncan and Hutchens fails to teach release of the analyte from the affinity reagent. However, because there is no such limitation in the claims under appeal, this argument is not persuasive.

C. Establishment of a Prima Facie Case of Obviousness by a Preponderance of the Evidence

Appellants state that the examiner has the initial burden of factually supporting a prima facie case of obviousness, and that additionally the examiner must prove her case by a preponderance of evidence with due consideration to the persuasiveness of any arguments in rebuttal. Additionally, appellants state, when the motivation to combine the teachings of the prior art references is not immediately apparent, it is the duty of the examiner to explain why the combination of the teachings is proper, keeping in mind that the fact that references can be combined or modified does not render the resultant combination obvious unless the prior art

suggests the desirability of the combination and/or modification. Lastly, the examiner is reminded that the suggestion to combine or modify should not be based on hindsight reconstruction.

In response, it is noted that Duncan expressly suggests that affinity chromatography be used in combination with MALDI when MALDI is used for the purpose of quantifying an analyte (see page 1094 of Duncan). Therefore, the motivation to modify the method of Duncan by the inclusion of a step of combining a specimen with an affinity reagent is expressly suggested by Duncan. The teachings of Nuwaysir provide the evidence that before the filing date of the instant application it was known in the art to combine affinity chromatography with MALDI in methods of detection of phosphopeptides, for example. The teachings of Hutchens provide evidence that before the filing date of the instant application it was known in the art to use affinity reagents (e.g., a metal ion, a protein, a peptide, a nucleic acid or a dye) in a step of combining an affinity reagent with a specimen so that an analyte of interest would be separated from other molecules that might be present in a specimen. Because Duncan suggests that in the practice of MALDI, quantification of an analyte will be improved if the specimen is first combined with an affinity reagent such as an affinity chromatography column there is no need for hindsight reconstruction. Therefore, appellants' assertion that the rejections over the prior art rely on hindsight reconstruction is simply false.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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